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Bronchopulmonary disposition of IV cefepime/taniborbactam (2–0.5 g) administered over 2 h in healthy adult subjects

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Introduction: Taniborbactam (formerly VNRX-5133) is an investigational β-lactamase inhibitor in clinical development in combination with cefepime for the treatment of MDR Gram-negative pathogens.

Objectives: To assess the safety profile and pulmonary disposition of 2–0.5 g cefepime/taniborbactam administered as a 2 h IV infusion every 8 h following three doses in healthy adult subjects.

Methods: In this Phase 1 trial, open-label study, plasma samples were collected over the last dosing interval, and subjects ($n=20$) were randomized to undergo bronchoalveolar lavage (BAL) at four timepoints after the last dose. Drug concentrations in plasma (total and free as determined by protein binding), BAL fluid and alveolar macrophages (AM) were determined by LC-MS/MS, and the urea correction method was used to calculate epithelial lining fluid (ELF) drug concentrations. Pharmacokinetic parameters were estimated by non-compartmental analysis.

Results: Mean (±SD) taniborbactam C_{max} and AUC_{0-8} in plasma were 24.1 ± 4.1 mg/L and 81.9 ± 13.9 mg·h/L, respectively. Corresponding values for cefepime were 118.4 ± 29.7 mg/L and 346.7 ± 71.3 mg·h/L. Protein binding was 0% for taniborbactam and 22.4% for cefepime. Mean taniborbactam concentrations (mg/L) at 2, 4, 6 and 8 h were 3.9, 1.9, 1.0 and 0.3 in ELF and 12.4, 11.5, 14.3 and 14.9 in AM, with corresponding $AUC_{0-8\ ELF}$ of 13.8 and $AUC_{0-8\ AM}$ of 106.0 mg·h/L. Cefepime $AUC_{0-8\ ELF}$ was 77.9 mg·h/L. No serious adverse events were observed.

Conclusion: The observed bronchopulmonary exposures of taniborbactam and cefepime can be employed to design optimal dosing regimens for clinical trials in patients with pneumonia.

Introduction

Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) continue to be prevalent among hospitalized patients and are associated with high mortality and healthcare costs.[1,2] Notably, HAP makes up approximately one in five healthcare-associated infections while the reported incidence of VAP ranges from 5% to 40% among patients undergoing mechanical ventilation.[1,3,4] Appropriate management of these infections in critically ill patients includes prompt administration of effective antibiotics and respiratory support. Effective antibiotics should provide activity against the most commonly isolated pathogens including Gram-positive (*Staphylococcus aureus*) and Gram-negative (*Pseudomonas aeruginosa*, Enterobacterales).[5] The Gram-negative pathogens in particular can often harbour multiple antimicrobial resistance mechanisms including β-lactamases, which can degrade and reduce the clinical utility of several currently approved β-lactam agents.[6,7]

Taniborbactam (formerly VNRX-5133) is an investigational bicyclic boronic acid-based β-lactamase inhibitor with *in vitro* activity against many clinically relevant Ambler Class A and C ESBL and cephalosporinases, Class A and D serine carbapenemases (e.g. KPC and OXA-48) and select Class B MBLs (e.g. NDM and VIM).[8–11] In one study utilizing a challenge set of carbapenemase-producing Enterobacterales (CPE; $n=247$) and carbapenem-resistant *Pseudomonas* species (CRP; $n=170$) from a variety of infection sites including respiratory tract infections, cefepime/

taniborbactam was the most active agent at an MIC of ≤8/4 mg/L (CPE: 97.6% susceptible; CRP: 67.6% susceptible) compared with ceftolozane/tazobactam, ceftazidime/avibactam, meropenem/vaborbactam and imipenem/relebactam.[12]

Taniborbactam is being developed in combination with cefepime as a broad-spectrum option for the treatment of serious Gram-negative infections. To that end, pharmacokinetic studies to assess taniborbactam concentrations at relevant sites of infection are needed. For lung infections, epithelial lining fluid (ELF) is considered to be the representative site of infection for extracellular pathogens, and the alveolar macrophage (AM) represents an important site for intracellular pathogens.[13,14] Characterizing drug exposure in these sites will allow pharmacokinetic/pharmacodynamic (PK/PD) assessments to guide selection of a clinical dose required to achieve the PK/PD targets. Therefore, the objective of this study was to determine pulmonary disposition and the safety profile of taniborbactam co-administered with cefepime in healthy adult subjects.

Methods

Study design

This was a Phase 1, open-label, single-site study (NCT03870490) that took place at the Clinical Research Center and Same Day SurgiCenter at Hartford Hospital (Hartford, CT, USA). The study consisted of a screening period lasting 56 days pre-dose, a 48 h dosing and drug sampling period, as well as a post-dosing safety evaluation (7 ± 2 days post-dose). Subjects received a dose of 2 g cefepime and 0.5 g taniborbactam co-administered together every 8 h via a 2 h infusion for a total of three doses. Taniborbactam (0.5 g/vial) and cefepime (2 g/vial) were supplied by Venatorx Pharmaceuticals, Inc (Malvern, PA, USA) and stored according to the manufacturer's recommendations until administration. Subjects were confined to the Clinical Research Center during administration of all three doses of study drug.

This study was approved by the Hartford Healthcare Institutional Review board and conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. Written informed consent was obtained for all subjects.

Study subjects

Non-smoking, healthy adult male and female subjects aged ≥18 years with a BMI ≥18.5 and ≤30 kg/m^2 were eligible for enrolment. Subjects were considered healthy based on physical examination, medical/surgical history, clinical laboratory tests and 12-lead ECG, all assessed in screening evaluations within 56 days of drug administration. Prior to dosing (Day −1), subjects underwent a physical and medical examination as well as clinical laboratory testing again to confirm that no clinical changes from the screening visit had occurred.

Key exclusion criteria included: allergy to cephalosporin or other β-lactam antibacterial drug or any component of taniborbactam for injection formulation, allergy to lidocaine, midazolam or other anaesthetics of similar classes, evidence or history of clinically significant medical abnormalities on physical examination, clinically significant ECG abnormality, including a mean QTcF of ≥450 ms or a short QTcF of <300 ms, predefined abnormal haematology and clinical chemistry tests, recent history of alcohol consumption exceeding 7 drinks/week for females or 14 drinks/week for men, use of tobacco- or nicotine-containing products from the day of screening through to the end-of-study evaluation, use of prescription or non-prescription drugs, vitamins or dietary supplements within 14 days prior to the first dose of study drug, except acetaminophen at doses of ≤3 g/day. Female subjects could not be lactating or pregnant. Males who were not surgically sterilized and females of childbearing potential agreed to use a recommended method of birth control throughout the course of the study and for 90 days after the last dose.

Plasma and BAL sample collection

Whole-blood sampling was conducted before dose 1 and at the following timepoints before and after dose 3: pre-dose (0 h; immediately before start of infusion), 2 (end of infusion), 2.25, 2.5, 3, 4, 6 and 8 h in K_2EDTA-containing vacutainers (Becton Dickinson and Company, Franklin Lakes, NJ, USA). Samples were centrifuged at 1500 × g for 10 min at 4°C and separated plasma was stored at −80°C until concentration determination.

All subjects were randomly assigned to undergo a single bronchoscopy with bronchoalveolar lavage (BAL) at 2, 4, 6 or 8 h after start of the third drug infusion (five subjects per timepoint). Subjects fasted for at least 6 h prior to the procedure and were then prepared for bronchoscopy with aerosolized lidocaine in the nares and oropharynx and 2% lidocaine jelly in the nasal passageway within 30 min of the procedure. The subjects underwent conscious sedation with IV injection of midazolam and fentanyl (per SurgiCenter standard of care) as needed. Each BAL was conducted with a fibre-optic bronchoscope (Olympus BF-Q190, Olympus America Inc., Center Valley, PA, USA) into the right middle lobe and utilized four aliquots of sterile 0.9% saline for instillation and aspiration as previously described.[15–18] The initial aliquot (50 mL) was discarded and the subsequent three aliquots (50 mL each) were stored on ice immediately after aspiration. The three aliquots were pooled (total volume recorded) and an aliquot obtained for complete cell count and differential. The remaining volume of pooled BAL was immediately centrifuged at 400 × g for 10 min, and the supernatant and cell pellet were separated. Supernatant aliquots were obtained to determine drug and urea concentrations. A blood sample was collected at the time of bronchoscopy to determine the plasma drug and urea concentrations. Water:formic acid (100:2, v/v) was added at a 1:1 ratio to all non-plasma samples to ensure taniborbactam drug stability prior to storage at −80°C until concentration determination.

Protein-binding determination

Protein-binding determination was performed for each subject at the 2 h plasma sampling timepoint (end of dose 3 infusion). Whole-blood samples at that timepoint were centrifuged as described above and one aliquot of plasma was frozen to serve as the total drug plasma concentration. The remaining plasma was transferred into six Centrifree ultrafiltration devices (Millipore Corporation, Billerica, MA, USA), which were then centrifuged for 25 min at 2000 × g at 4°C. The ultrafiltrate samples (cefepime, $n = 3$ replicates; taniborbactam, $n = 3$ replicates) with 1:1 addition of water:formic acid (100:2, v/v) for each subject were frozen at −80°C until concentration determination. Each ultrafiltrate concentration represented the free drug plasma concentration and the three replicates per drug were averaged for each subject. Drug-free fraction was calculated using:

$$\text{Free fraction} = \text{Concentration}_{\text{ultrafiltrate}}/\text{Concentration}_{\text{plasma}}$$

The free fraction was used to calculate protein unbound plasma drug concentrations for each subject.

Pharmacokinetic analysis

Taniborbactam and cefepime concentrations were assayed using validated LC-MS/MS methods. The lower limit of quantitation (LLOQ) was 100 ng/mL for both taniborbactam and cefepime in plasma, and 5.00 ng/mL and 3.00 ng/mL for taniborbactam and cefepime, respectively, in ELF. Assay accuracy and precision were demonstrated for all assays in the validations.[19] Urea concentrations in plasma and BAL fluid were

determined by Keystone Bioanalytical, Inc. (North Wales, PA, USA) using validated LC-MS/MS methods.

The ELF volume and drug concentration were calculated by the urea dilution method and described below:[20]

$$V_{ELF} = V_{BAL} \times (Urea_{BAL}/Urea_{PLASMA}),$$

where V_{ELF} is the volume of ELF sampled by BAL, V_{BAL} is the volume of BAL fluid recovered from aspiration, $Urea_{BAL}$ is the concentration of urea in the BAL fluid and $Urea_{PLASMA}$ is the concentration of urea in the plasma. The concentration of the antibiotic in ELF (ABX_{ELF}) was determined by the following relationship:

$$ABX_{ELF} = ABX_{BAL} \times (V_{BAL}/V_{ELF}),$$

where ABX_{BAL} is the concentration of the antibiotic determined in the BAL fluid sample.

The number of AM within the BAL fluid was determined from the mean proportion of histiocytes and monocytes present in two manual cell counts, and the total volume of these cells in the cell pellet was calculated by using a mean AM cell volume of 2.42 μL/10^6 cells.[21] To determine the total amount (Amt) of drug in the cell pellet, the following equation was used:

$$Amt_{PELLET} = ABX_{PELLET} \times V_{PELLET},$$

where ABX_{PELLET} is the concentration of drug within the reconstituted cell pellet and V_{PELLET} is the volume used to reconstitute the cell pellet. The amount of drug in the AM could then be calculated using the following equation:

$$Drug_{AM} = Amt_{PELLET}/(\text{mean AM in BAL} \times V_{AM}),$$

where V_{AM} is the mean cell volume of an AM (2.42 μL/10^6 cells). AM drug concentrations were determined for taniborbactam only.

Taniborbactam and cefepime plasma pharmacokinetics were described by non-compartmental methods using Phoenix WinNonlin (Certara, Princeton, NJ, USA). Estimated pharmacokinetic parameters included the maximum concentration (C_{max}), AUC over the dosing interval (AUC_{0-8}) calculated using the linear/log trapezoidal rule, the free drug exposure ($fAUC_{0-8}$) calculated by correcting concentrations for protein binding, the volume of distribution at steady state (V_{ss}), and CL. PK parameters in ELF (C_{max}, T_{max} and AUC_{0-8} by linear/log trapezoidal rule) were calculated manually based on mean ELF concentrations. Drug penetration was estimated by the ratio of the AUC_{0-8} for ELF or AM to the mean $fAUC_{0-8}$ in plasma.

Safety assessment

Safety and tolerability assessments included adverse event (AE) recording, physical examinations, clinical laboratory tests, vital signs and ECGs. Investigators assessed each subject for observed and reported AEs throughout the duration of the study (i.e. from the time of signed informed consent until the final evaluation was completed 7 days post-dose). AE reporting criteria were adapted from the criteria in FDA Guidance (2007; 'Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials') and the US DHHS: Common Terminology Criteria for AEs v4.0.

Results

Study subjects

The study population consisted of 20 healthy adults ranging in age from 23 to 62 years (mean age, 34.8 years). Of these subjects, 14 were male; 15 were of Caucasian race, 4 were of Black or African-American race, and 1 was of Asian race. Three subjects were of Hispanic ethnicity. The mean (±SD) for weight and BMI were 72.8 (14.0) kg and 24.6 (2.9) kg/m^2, respectively. Mean estimated CL_{CR} (±SD) on Study Day −1 was 115.7 (26.2) mL/min.

Pharmacokinetics and protein binding

The pharmacokinetic population included all subjects ($n = 20$) who received three doses of study drug and had both plasma and BAL samples collected. Mean (±SD) total plasma concentration–time profiles for taniborbactam and cefepime are displayed in Figure 1. Drug concentrations taken immediately prior to the third dose (pre-dose) and at 8 h after the third dose were similar: taniborbactam, 3.3 mg/L (pre-dose) versus 3.2 mg/L (8 h); cefepime, 11.4 mg/L (pre-dose) versus 10.7 mg/L (8 h), indicating that concentrations were at steady state. The plasma pharmacokinetics of each drug are listed in Table 1.

Plasma protein-binding results indicated 100% of taniborbactam was unbound (range: 99.3% to 100%). Similar analysis with cefepime demonstrated an unbound range of 58.1% to 94.9% with a mean of 77.6% unbound. This resulted in a taniborbactam and cefepime steady-state plasma $fAUC_{0-8}$ (coefficient of variation %, CV) of 81.9 (17%) and 262.6 (12.5%) mg·h/L, respectively. The individual concentrations of cefepime and taniborbactam in free plasma, ELF and AM at the four BAL sampling timepoints are detailed in Table 2 and illustrated in Figures 2 and 3, respectively. Of note, taniborbactam BAL concentrations in two subjects at the 8 h timepoint were below the LLOQ and the ELF concentration was considered to be 0 mg/L for pharmacokinetic analysis.

The mean AUC_{0-8} values based on ELF and AM concentrations of taniborbactam of all 20 subjects were 13.8 and 106.0 mg·h/L, respectively. Taniborbactam disposition into the ELF and AM using respective composite AUC_{0-8} compared with the mean $fAUC_{0-8}$ in plasma was approximately 0.17 and 1.29, respectively. Similarly, the disposition of cefepime into ELF was 0.30.

Safety and tolerability

All 20 subjects received three doses of study drug and were included in the safety population. Overall, cefepime and taniborbactam co-administration was well tolerated with no serious AEs or deaths reported. Treatment-emergent AEs (TEAEs) were reported by 14 subjects during the study. The most common AE, occurring in six subjects, was leucocytosis. The other TEAEs occurring in at least two subjects were: hyperbilirubinaemia, dizziness, chills, increased blood creatinine, increased international normalized ratio, headache and rash erythematous. The bronchoscopy and BAL procedures were well tolerated by all subjects, with conscious sedation required in two subjects. All TEAEs that were considered possibly related to study drug were mild in severity and no patients discontinued the study due to an AE.

Discussion

Determining drug concentrations at sites of infections other than serum is important, given that these sites or compartments are bordered by diffusional barriers that can influence drug pharmacokinetics and exposure.[13,14,22] These measured drug

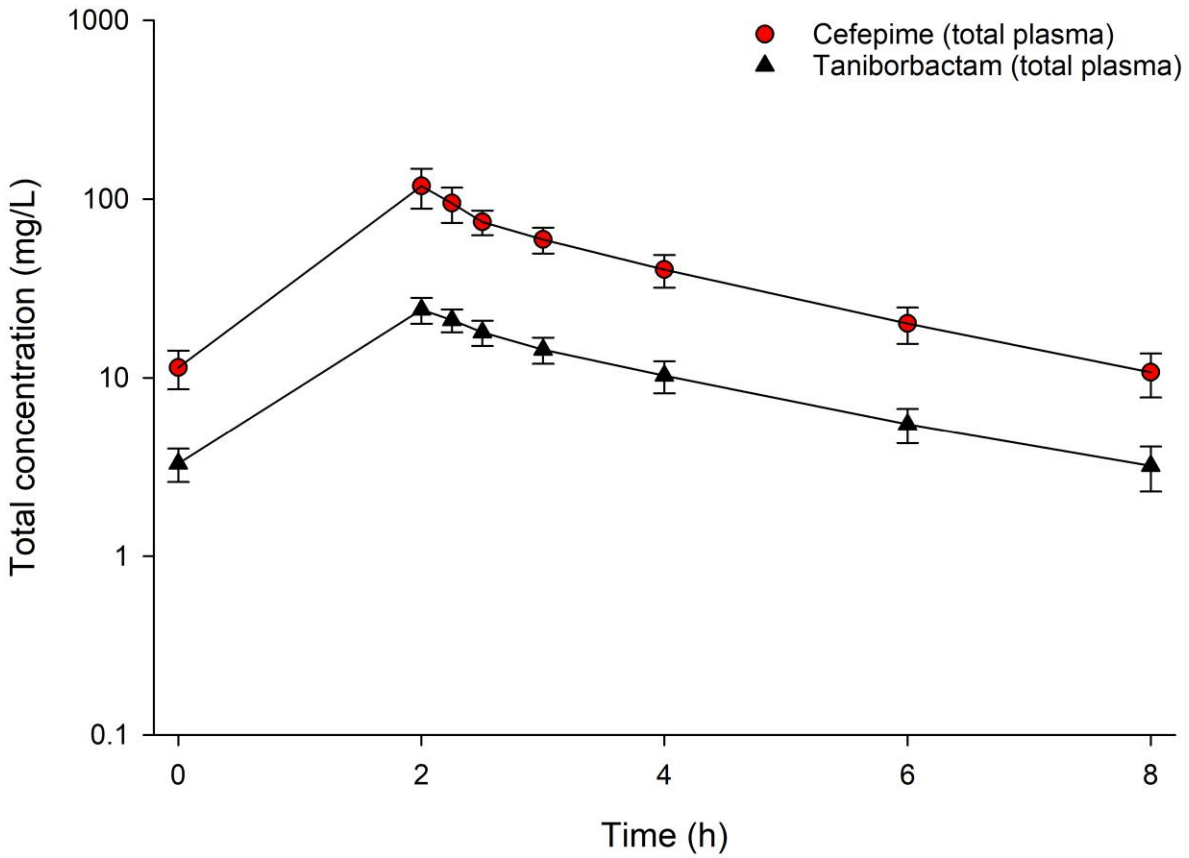

Figure 1. Concentration–time profiles (mean ± SD; 20 subjects) for cefepime and taniborbactam in total plasma after the third dose of 2 g cefepime—0.5 g taniborbactam administered as a 2 h IV infusion every 8 h.

Table 1. Steady-state plasma pharmacokinetic parameter estimates from 20 healthy volunteers receiving cefepime/taniborbactam 2–0.5 g

	Mean (SD)	
Pharmacokinetic parameter	Taniborbactam	Cefepime
C_{max} (mg/L)	24.1 (4.1)	118.4 (29.7)
T_{max} (h)	2.01 (0.01)	2.0 (0.1)
AUC_{0-8} (mg·h/L)	81.9 (13.9)	346.7 (71.3)
$fAUC_{0-8}$ (mg·h/L)	81.9 (13.9)	262.6 (32.7)
V_{ss} (L)	20.3 (3.0)	17.3 (3.2)
CL (L/h)	6.3 (1.0)	6.0 (1.2)
$t_{½}$ (h)	2.3 (0.3)	2.0 (0.2)

f, free (protein unbound),; CL, total body clearance; $t_{½}$, terminal half-life.

concentrations at the sites where bacterial infections occur allows for integration into PK/PD analysis using PD targets obtained from pre-clinical *in vitro* studies and animal infection models.[23] Subsequent population pharmacokinetic modelling and simulation will assist in developing dosage regimens that ensure clinical efficacy and minimize drug resistance development.[24]

Plasma taniborbactam concentrations achieved in this study were similar to those seen in the recently published first-in-human taniborbactam pharmacokinetic Phase 1 study.[25] The multiple-ascending-dose portion of that study evaluated 2 h IV infusions of 250, 500 or 750 mg taniborbactam every 8 h over 10 days without cefepime co-administration. The mean plasma AUC_{0-8} of taniborbactam 500 mg in that study after 10 days was 89.1 mg·h/L (C_{max}, 26.5 mg/L), whereas our observed AUC_{0-8} was 81.9 mg·h/L (C_{max}, 24.1 mg/L). The ratio of free plasma AUC_{0-24} to MIC ($fAUC_{0-24}$/MIC) has been found to be the PK/PD parameter that best correlates with taniborbactam efficacy in a murine thigh infection model.[26] When these cefepime and taniborbactam plasma exposures are paired with *in vitro* activity against Enterobacterales, *P. aeruginosa* and *Stenotrophomonas maltophilia* isolates, PK/PD analysis from a complicated urinary tract infection model predicts a high likelihood of *in vivo* efficacy (up to a cefepime/taniborbactam MIC of 32 mg/L).[8,26,27]

Over the 8 h dosing interval, the taniborbactam mean C_{max} and composite AUC_{0-8} were 3.9 mg/L and 13.8 mg·h/L for ELF, and 14.9 mg/L and 106 mg·h/L for AM, respectively. The mean ratio of ELF to free plasma AUC was 0.17. The concentration–time profile of taniborbactam in AM did not mirror that of plasma or ELF. The C_{max} for AM concentrations occurred at the last sampling

Table 2. Taniborbactam and cefepime steady-state concentrations in plasma, ELF and AM at time of bronchoscopy and BAL

	Concentration (mg/L)[a]						
	Taniborbactam				Cefepime		
Time of BAL (h)	Total plasma	Free plasma	ELF	AM	Total plasma	Free plasma	ELF
2	22.7 (15.5)	22.7 (15.5)	3.9 (26.7)	12.4 (56)	110 (28.9)	84.8 (15.3)	19.9 (23.3)
4	11.7 (15.8)	11.7 (15.8)	1.9 (30.8)	11.5 (20.7)	44.6 (14.7)	36.8 (17.8)	10.6 (33.6)
6	5.8 (15.2)	5.8 (15.2)	1.0 (24.5)	14.3 (46)	21.5 (12.8)	16.0 (7.2)	6.2 (25.4)
8	3.5 (30.2)	3.5 (30.2)	0.3 (95.8)	14.9 (19.3)	11.6 (29.6)	8.1 (17.6)	3.1 (43.8)

[a]Data are shown as mean (CV%).

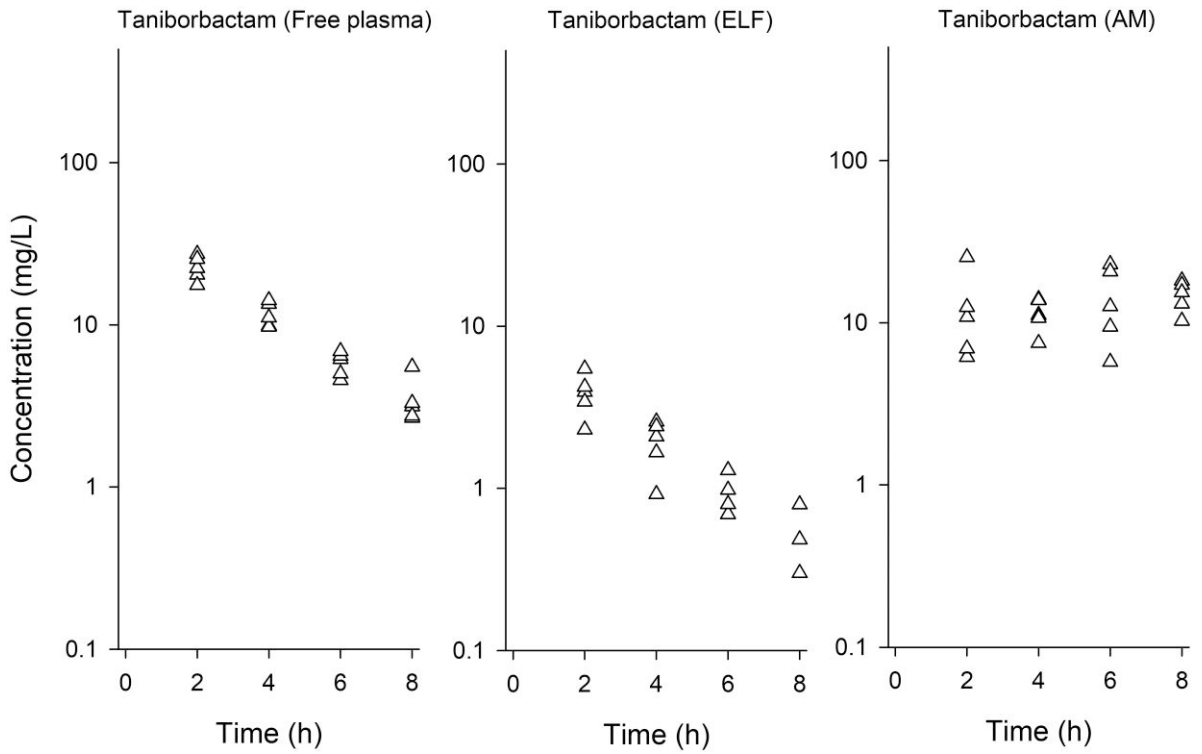

Figure 2. Individual concentrations of taniborbactam in free (protein unbound) plasma, ELF and AM at the time of bronchoscopy after the third dose of 2 g cefepime—0.5 g taniborbactam administered as a 2 h IV infusion every 8 h.

timepoint (8 h post-dose) and concentrations remained relatively constant over the 8 h dosing interval. The mechanism of accumulation in AM cells observed with taniborbactam has yet to be determined but the AM concentration profile from bronchopulmonary studies with another boronic β-lactamase inhibitor, i.e. vaborbactam, follows a similar pattern.[28] Drug concentrations in AM are important for antimicrobial agents targeting intracellular respiratory pathogens such as *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae* and *Legionella pneumophila*. The significance of these intracellular observations has yet to be determined for cefepime/taniborbactam, which is being developed for the treatment of infections caused by β-lactamase-producing CRE and CRP, which have predominantly extracellular life cycles.[8,29]

The pharmacodynamic efficacy target has yet to be determined for cefepime/taniborbactam based on ELF exposures, but preliminary lung infection model studies in mice using plasma exposures have demonstrated several-fold reduction in bacterial burden relative to cefepime monotherapy against cefepime-resistant isolates, including serine-carbapenemase producers.[30,31] However, it is important to recognize that drug disposition into lung varies across species, and in this case between mice and humans, potentially limiting extrapolation and clinical translation. To overcome this, Abdelraouf *et al.*[31] performed a series of murine studies to encompass a variety of taniborbactam lung exposures thus reflecting different penetration ratios. This was achieved through

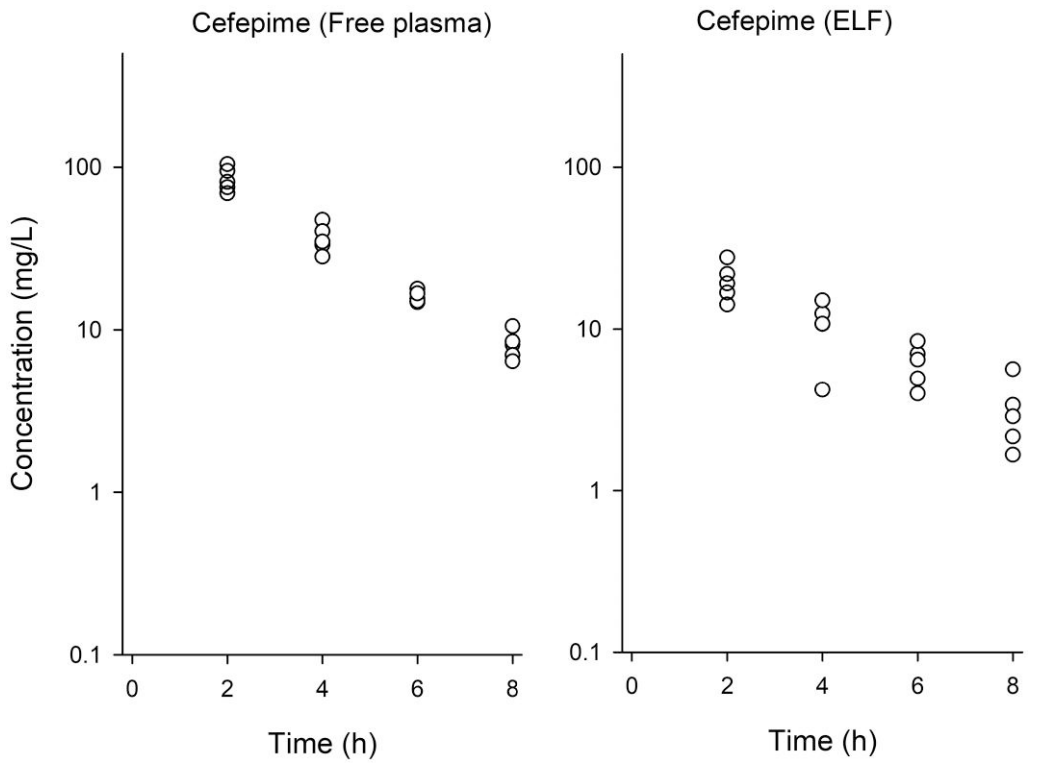

Figure 3. Individual concentrations of cefepime in free (protein unbound) plasma and ELF at the time of bronchoscopy after the third dose of 2 g cefepime—0.5 g taniborbactam administered as a 2 h IV infusion every 8 h.

dose-ranging experiments using fixed cefepime exposures but varying taniborbactam exposures (ranging from 1.56% to 100% of human plasma exposures). Taniborbactam AUC exposures as low as 6.25% of human plasma exposures in combination with cefepime demonstrated bacterial killing in the lung, with a median taniborbactam *f*AUC_{0-24}/MIC plasma value associated with the 1 log kill endpoint of 4.03 and 3.02 among Enterobacterales and *P. aeruginosa*, respectively.[31] These data provide support for further PK/PD and clinical studies to ascertain the potential of cefepime/taniborbactam as a therapeutic agent for treating pneumonia caused by MDR Gram-negative pathogens.

Conclusions

In summary, BAL studies in healthy subjects have become an important means to determine the bronchopulmonary pharmacokinetics of antimicrobials and can be instrumental in de-risking Phase 3 pneumonia clinical trials. In the current trial, cefepime and taniborbactam co-administration was well tolerated with no serious AEs. Data generated in this study have provided insights into the bronchopulmonary disposition of taniborbactam, a novel β-lactamase inhibitor with activity against a variety of serine-β-lactamases and MBLs. Ultimately, the bronchopulmonary exposures of the compound will be influenced by the dose and/or duration of infusion selected for use in the clinical programme.

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